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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/738,413	12/17/2003	Ralph R. Binetti	SC66U-US	8915

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EXAMINER	
BOWMAN, AMY HUDSON	
ART UNIT	PAPER NUMBER
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/30/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/738,413	BINETTI ET AL.	
	Examiner	Art Unit	
	Amy H. Bowman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *40 and 41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/13/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 1/19/07 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 10/18/2005 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-41 are pending in the instant application. Claim 39 will be examined with the claims of Group I and is rejected for the same reasons as claim 38. It is noted that the restriction of claim 39 was not argued in the response to the restriction filed on 8/22/2005. Claims 40 and 41 are withdrawn, as being drawn to a non-elected invention.

Upon further consideration, the restriction requirement between human and mouse tyrosinase mRNA mailed on 8/28/2006 has been withdrawn because the claims do not recite human or mouse in the alternative, but are rather directed to siRNA oligomers that are specific for human "and" mouse tyrosinase mRNA. Therefore, the claims are limited to sequences that are specific for both sequences only.

This application contains claims 40 and 41, as well as SEQ ID NOs: 3-6 (sequences other than SEQ ID NO: 1 or its complement SEQ ID NO: 2), drawn to an invention nonelected without traverse. A complete reply to the final rejection must

include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant's arguments filed on 6/2/2006, with respect to the rejection(s) of claim(s) 1-38 under 35 U.S.C. 112, first paragraph for written description have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, the claims remain rejected under 35 U.S.C. 112, first paragraph, for lack of enablement, as explained below.

Response to Arguments--Claim Rejections - 35 USC § 112, first paragraph

Claims 1-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. Claims 1-38 stand rejected for the reasons of record set forth in the office action mailed 10/18/2005. Claim 39 is rejected for the same reasons.

Applicant asserts that the examiner has not provided sufficient reasons why one would not expect a correlation between the *in vitro* results provided and the *in vivo* effects of the claimed invention. Applicant points to MPEP 2164.02 to conclude that the initial burden is on the examiner to give reasons for a conclusion of lack of correlation for an *in vitro* or an *in vivo* animal model example and the *in vivo* effects of the claimed invention.

Importantly, MPEP 2164.02 explains that an *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example correlates with a disclosed or claimed method invention. If there is no correlation, then

the examples do not constitute "working examples". Applicant has not provided a correlation between inhibiting tyrosinase expression and prevention, amelioration, reduction and/or elimination of the broad genus of instantly recited conditions, which include any unwanted skin condition.

MPEP 2164.02 explains that if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. In the instant case, applicant has not provided a particular model that is recognized as correlating siRNA oligomers specific for mouse and human tyrosinase mRNA to the desired effect on the broad genus of conditions that are instantly recited. Additionally, applicant has not provided any correlation with the instant method and a resultant prevention or elimination of unwanted skin conditions, as instantly recited.

The instant specification, nor the prior art, are enabling for treating hyperpigmentation or any other unwanted pigmentation or skin disorder via introducing any siRNA oligomer specific for any portion of tyrosinase mRNA because introducing dsRNA into a cell or organism is neither routine nor predictable. Additionally, applicant is not only claiming treatment effects of a vast genus of skin conditions, but is also claiming prevention effects, which have not been demonstrated by applicant or the prior art. Neither the instant specification nor the prior art exhibit prevention of any of the claimed disorders via introduction of siRNA oligomers specific for tyrosinase. Applicant has not demonstrated that introduction of a siRNA oligomer specific for tyrosinase would prevent any unwanted skin condition or unwanted pigmentation. Thus, one of

skill in the art could not practice the invention commensurate in scope with the claims without undue, trial and error experimentation and therefore, claims 1-39 are not enabled.

MPEP 2164.08 explains that the questions of enablement are evaluated against the claimed subject matter and the focus of the examination inquiry is whether **everything** within the scope of the claim is enabled. Applicant is claiming treatment effects of any unwanted pigmentation or skin disorder via administering any siRNA oligomer specific for mouse and human tyrosinase. The specification is not enabling for treatment, amelioration, reduction and/or elimination of such a vast genus of disorders via administering such a broad genus of siRNA oligomers and certainly is not enabling for prevention of any such disorder.

Furthermore, applicant argues that the art relied upon by the examiner does not establish unpredictability of siRNA delivery to cells *in vivo*. Specifically, applicant argues that Caplen is not analogous to the current invention because Caplen is referring to longer dsRNA. Contrary to applicant's argument, Caplen refers to inhibition of target gene expression via RNAi, which is the focus of the instant invention. The obstacles faced by the dsRNA molecules taught by Caplen et al. are known to be the same obstacles faced by shorter dsRNA molecules.

This is further evidenced by Caplen (Expert Opin Biol Ther, 2003 Jul, 3(4), pp. 575-86), who points out that, "Many of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous gene therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell

type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system..." (see page 581). These teachings support the unpredictability of nucleic acid delivery *in vivo*.

Applicant argues that although Zhang et al. teach that delivery of siRNA to mammalian cells is not simple, Zhang et al. provides examples of effective delivery of siRNA to mammalian cells. The examiner has not asserted that there have not been effective delivery of siRNA to mammalian cells, but rather asserts that such delivery is unpredictable. The instant claims are directed to topical administration of siRNA oligomers specific for tyrosinase, which is not commensurate in scope with the teachings of Zhang et al. that do not discuss topical administration. Zhang et al. teach specifically teach that although dsRNA can be delivered to *C. elegans* by feeding or soaking, effective delivery of siRNAs to mammalian cells will not be so simple.

Applicant asserts that a connection between the instantly recited disorders and tyrosinase expression has been firmly established and points to art regarding tyrosinase and hyperpigmentation. Applicant further argues that Hartmann et al., relied upon by the examiner, teaches that the pathophysiology of hypopigmentary disorders is still poorly understood and is therefore irrelevant to the instant claims that are directed to hyperpigmentary disorders. Contrary to applicant's assertions, the instant claims are directed to a method of treating hyperpigmentation, or other unwanted pigmentation, or other unwanted skin condition. Applicant's arguments seem to be directed to hyperpigmentation alone, which is not commensurate in scope with the instant claims. Therefore, not only does the prior art demonstrate unpredictability of

attenuating/inhibiting expression of a target gene *in vivo* by RNA interference (RNAi), but the prior art also evidences the unpredictability of treatment of skin disorders, as evidenced by Hartmann et al.

Although applicant asserts that a connection between the instantly recited disorders and tyrosinase expression has been firmly established and points to art regarding tyrosinase and hyperpigmentation, the instant claims are much broader in scope, directed to treating any unwanted pigmentation or any unwanted skin condition.

Thus, while the specification is enabling for the *in vitro* examples set forth in the specification, the specification is not enabling for introducing any siRNA for human and mouse tyrosinase mRNA in any cell or animal as the art of attenuating gene expression by introducing dsRNA into a cell or organism is neither routine nor predictable. Additionally, applicant is not only claiming treatment effects, but is also claiming prevention. Neither the instant specification nor the prior art exhibit prevention of any of the claimed disorders via introduction of siRNA oligomers specific for tyrosinase. Applicant has not demonstrated that introduction of a siRNA oligomer specific for tyrosinase would prevent an unwanted skin condition or unwanted pigmentation. Thus, one of skill in the art could not practice the invention commensurate in scope with the claims without undue, trial and error experimentation and therefore, claims 1-39 are not enabled.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is (571) 272-0755.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Amy H Bowman
Examiner
Art Unit 1635

JON E. ANGELL, PH.D.
PRIMARY EXAMINER

AHB